Embryogenesis and Fetal Flow

Introduction

The heart—four chambers, four valves, two huge arteries, and several large veins—is derived from one long tube. That tube needs to **fold** to bring the structures to where they need to be. More importantly, that tube needs to be **divided**. The **truncus arteriosus** (one common artery tube) needs to be divided into the pulmonary artery and aorta. The **common ventricle** needs to be divided into the left and right ventricles. The **common atrium** needs to be divided into the left and right atria. The atria need to be divided from their respective ventricles. The **outflow tract** must be divided into two outflow tracts and connected to the appropriate great arteries. That is the subject of this entire lesson—septation and twisting of a hollow tube into the adult heart. All of this must be achieved in utero, without lungs. This subject is very difficult to master. The intro is kept brief because it is too difficult to adequately project what is going to happen without already having the vocabulary. Get ready for some immersion learning.

Because the embryological structures share their names with the things they are destined to become, we use specific nomenclature. "Primordial" means "at the stage of the heart tube." "Common" means "after the heart-folding is complete." "Adult" means "after embryogenesis is complete." This primarily applies to the ventricles and atria, but we will use this terminology if we need to distinguish something by its embryological chronology.

Heart Folding and Destiny of Heart Muscle

Fertilization, implantation, a couple of weeks go by, and HOORAY! HEART TUBE! There are many (very important) processes that transform the extraembryonic mesoderm (we want you to be intimidated by those words) into the blood vessels of the placenta and transform the intraembryonic mesoderm (these ones, too) into the blood vessels of the fetus and the fetal heart. We skipped them in order to start with what matters. If anything goes wrong with the heart in the first 3 weeks, the embryo will not survive to this point. We begin our discussion at the **heart tube.** At this stage, it looks nothing like a heart. It is just a tube, yet the regions of that tube are already established, already destined to become the final heart structures.

The heart tube can be divided (by embryologists, not embryogenesis) into five general regions. They are continuous and their locations along the heart tube determine their ultimate destiny in the adult heart. At the top is the primordial **truncus arteriosus**. This is the artery side of the heart tube, destined to become the adult **pulmonary artery** and **aorta** (the great arteries). The primordial **bulbus cordis** is next, destined to become the adult **ventricular outflow tract** and adult **right ventricle**. The **primordial ventricle** (the region of the gut tube) will become the adult **left ventricle**. Next is the **primordial atrium,** which will give rise to the common atrium and subsequently the **adult atria**. Last is the venous side of the heart tube, the primordial **sinus venosus,** which will become the adult **pulmonary vein**, adult **superior and inferior venae cavae**, and adult coronary sinus.

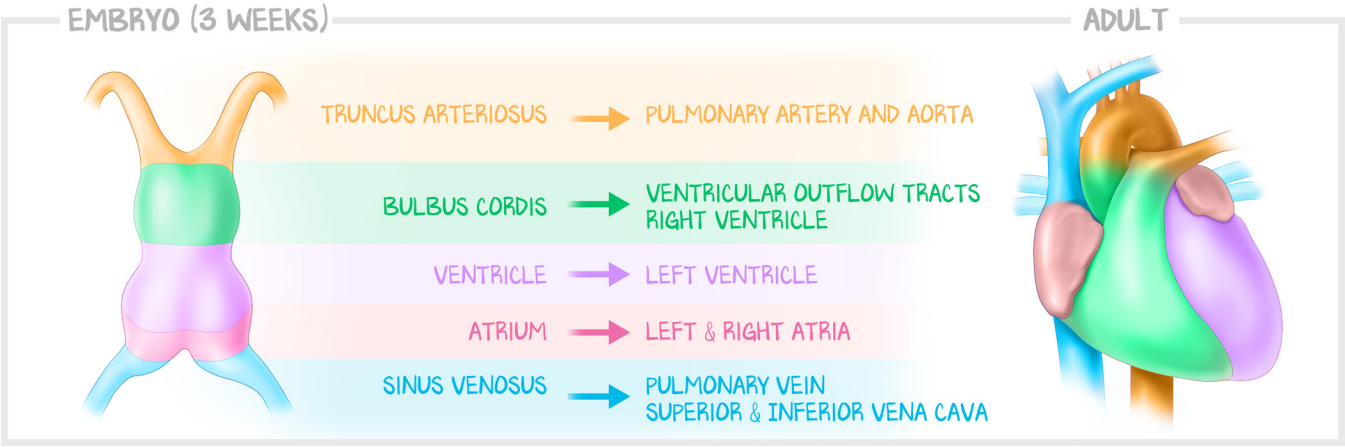

Figure 1.1: Cardiac Fetal Heart Tube
The destiny of different regions of the heart tube is already established. As the tube twists, turns, and grows, the nomenclature changes, but the destinies do not.

The **top of the tube** is destined to become arteries and the ventricles to which they connect. The **bottom of the tube** is destined to become the veins and the atria to which they connect. The heart tube must **fold** to bring the atria and the great veins above the ventricles. The arteries are already above their corresponding ventricles.

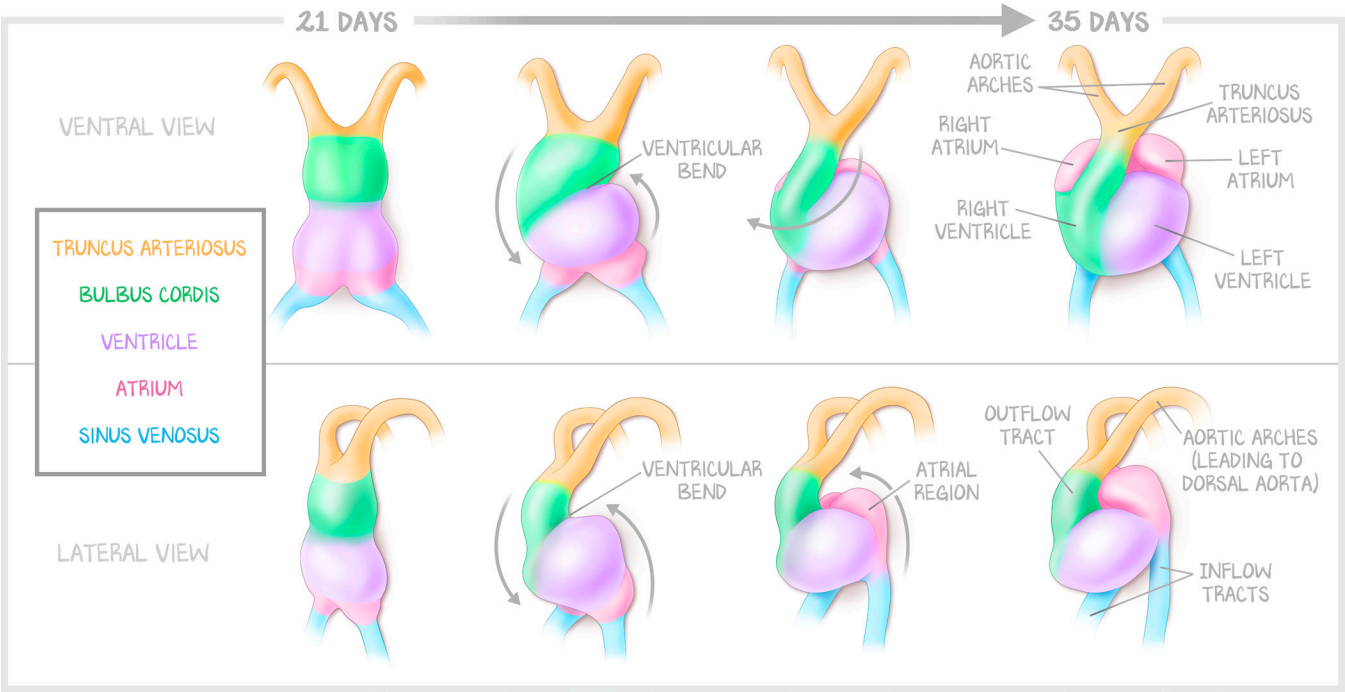

Figure 1.2: Fetal Heart Folding
You do not have to master this content. Heart folding involves the folding and growing of the heart into the appropriate orientation. By day 35 in utero, the structures are already in their final position. Then, they just need to grow in size and divide.

Separating Top From Bottom: Endocardial Cushions

The bulbus cordis, primordial ventricle, and primordial atrium all fuse to make one giant chamber. That chamber consists of one **common atrium** and one **common ventricle**. The common atrium is on top, the common ventricle below. There is no left-right septation of the common atrium, no left-right septation of the common ventricle, and no top-down septation of the common atrium from the common ventricle. The first separation is the common atrium from the common ventricle. The common atrium is separated from the common ventricle by the formation of the **atrioventricular septum**, which starts with endocardial cushions.

At this point, the **endocardial cushions** grow towards one another and fuse, forming one common endocardial cushion and the atrioventricular septum that **separates top from bottom**. They also grow and fuse so that the one common **atrioventricular canal** is divided into left and right **atrioventricular canals**, one on either side of the now singular endocardial cushion. The cells of the endocardial cushions are derived from **neural crest cells**.

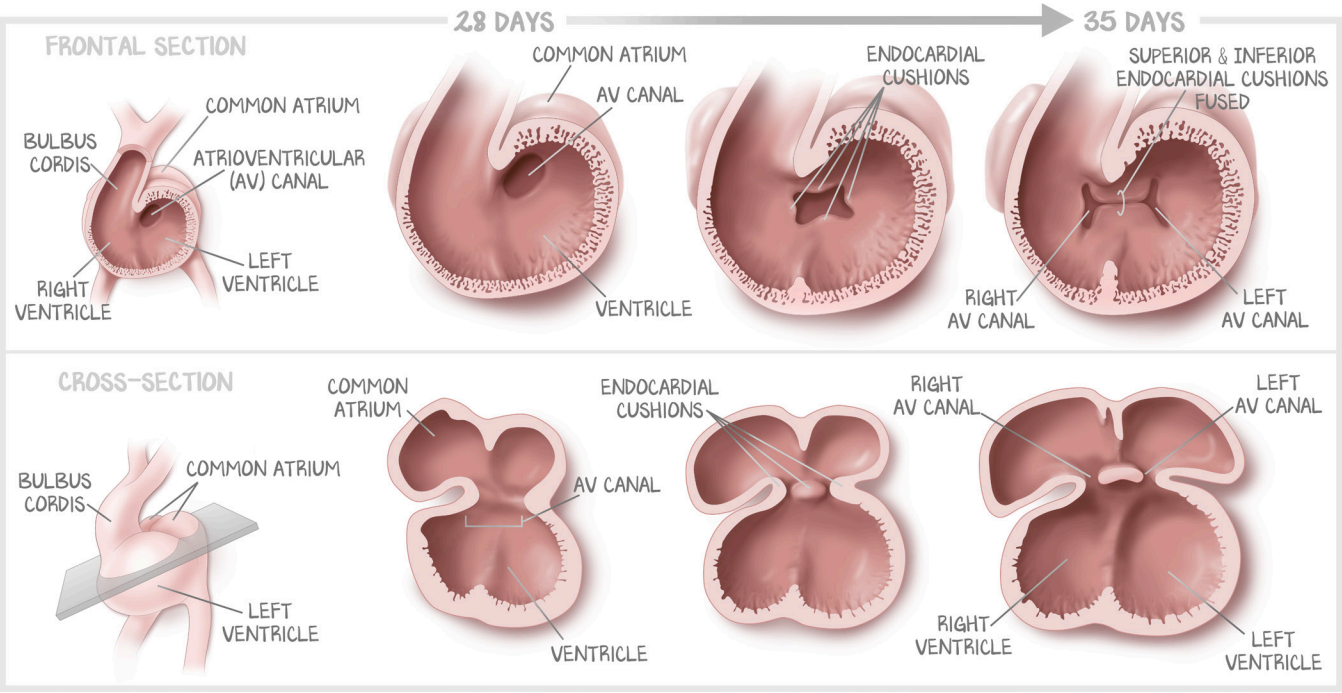

Figure 1.3: Endocardial Cushions
The frontal view removes the front of the bulbus cordis and ventricle to show the common atrioventricular (AV) canal and endocardial cushions moving fusing into one common endocardial cushion with AV canals (which will become the valves) on either side. The cross-section allows for visualization of the common atrium (on top) and common ventricle (on the bottom) being separated by the ingrowth of the endocardial cushions.

Separating Left from Right: Interatrial Septa

There is one common atrium sitting on top of one common ventricle, separated by an atrioventricular septum but connected by two atrioventricular canals. This next part describes how the common atrium is divided into the left and right atria. Be careful with the nomenclature. A septum is a wall. An ostium is a gap. A foramen is neither. Primum means first, and secundum means second. The relationships between the structures have nothing to do with their names. For example, both the ostium primum and ostium secundum are in relation to the septum primum. Look at Figure 1.4 as you follow along with the text.

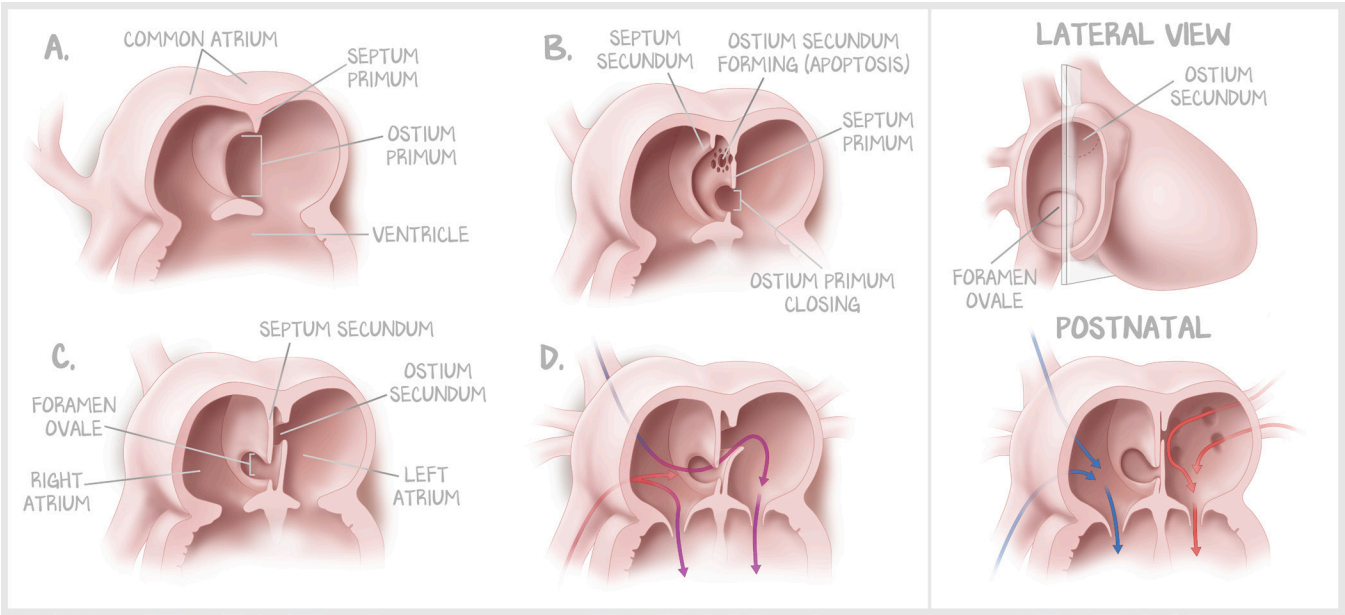

Figure 1.4: Atrial Septation
This model has the anterior of the atria removed, as shown in the lateral view to the right. You cannot see the complete atrial septum, but you can see enough of it to understand what is about to happen. After you see Dr. Williams' simplified version on the board, you can look at this again and decide which one makes more sense to you.

(A) The common atrium begins to be divided by the septum primum, which grows from the posterior superior wall, growing both forward and down from the roof of the atrium. The **septum primum** is the tissue, and the gap left between the septum primum and the endocardial cushion is the **ostium primum**. The ostium primum does not "form," it is merely the gap in the tissue that was already present at the end of the formation of the atrioventricular septum.

(B) Then, the **septum secundum** also begins to form from the posterior of the common atrium. As the septum primum approaches the endocardial cushion, as the ostium primum is nearly closed off, the **ostium secundum** forms in the **septum primum** via apoptosis. There must always be a connection from the right atrium to the left atrium during development, and the formation of the ostium secundum allows for that.

(C) The septum primum does not grow to fill the common atrium completely. It leaves a **foramen ovale**. The ostium secundum forms **above the foramen ovale**, leaving tissue from the septum primum obscuring the foramen ovale and tissue of the septum secundum obscuring the ostium secundum. Not depicted in this illustration is that, as the septum primum encroaches on the endocardial cushions, the **neural crest cells migrate to meet it**. The mesoderm-derived myocardial septum primum completes the interatrial septum by waiting for the neural crest cells to migrate to it.

(D) Because the foramen ovale and the flap of the septum primum are not affixed to anything (the ostium secundum is just a space above the flap of the septum primum), as blood enters the atrium from the inferior vena cava, it is projected toward the foramen ovale and pushes open the septum primum flap.

(POSTNATAL) After birth, the pressure in the pulmonary vasculature drops as the vessels (and alveoli) open. The increased left atrial pressure is greater than the right atrial pressure, and the flap closes, often fusing with the septum secundum.

Separating Left From Right: Interventricular Septum

Thankfully, interventricular septum formation is less complex than interatrial septum formation.

The **adult interventricular septum** not only divides the ventricles into left and right but also carries nerve conduction fibers, myocytes, and blood vessels. The adult interventricular septum has a short membranous portion at the outflow tracts and a long muscular portion from the apex to the outflow tracts. The **muscular portion** is derived from **mesoderm**; the **membranous portion** is derived from ectoderm, from **neural crest cells**.

The **embryonic muscular interventricular septum** grows from the base of the common ventricle toward the endocardial cushion, dividing the ventricles from the bottom up. The interventricular septum is completed by **neural crest cell migration** from the **aorticopulmonary septum**. The fusion of the neural-crest-derived aorticopulmonary septum with the mesoderm-derived embryonic ventricular septum completes the adult interventricular septum. Don't worry, we're just about to discuss the aorticopulmonary septum.

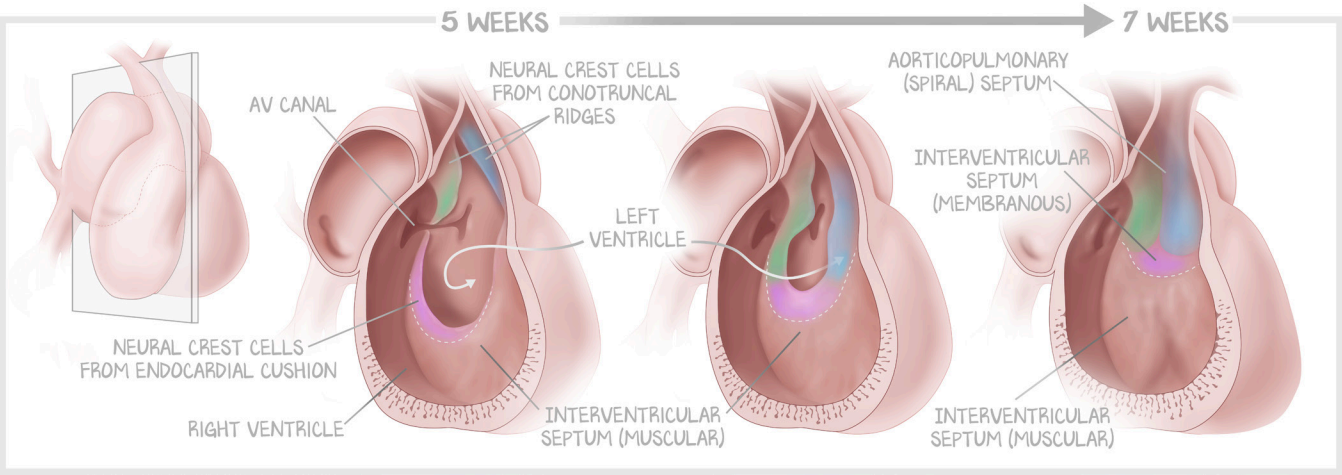

Figure 1.5: Ventricular Septation
This illustration is shown from an oblique lateral angle, from the right ventricle with the lateral wall removed. Behind the septum is the left ventricle (indicated by the white arrows). On our side of the septum is the right ventricle. The atrioventricular canals are each ventricle's connection to its atrium. Neural crest cell migration from the endocardial cushion meets the muscular interventricular septum as it rises between the right and left ventricle (purple). Separately, neural crest cells from the conotruncal ridges (future aorticopulmonary septum, named correctly, but not something we want you to remember) migrate to become the aorticopulmonary septum. The aorticopulmonary septum neural crest cells should meet the endocardial cushion neural crest cells to become the membranous portion of the interventricular septum, dividing one common outflow tract into two, dividing one common ventricle into two, and dividing the truncus arteriosus into two great arteries.

This has divided the cardiac tube into two separate systems. The pulmonary-trunk-right-ventricle connected to the right atrium, and the aorta-left-ventricle connected to the left atrium. That sounds pretty easy. But we need a twist. And that makes it hard.

The Aorticopulmonary Septum, With a Twist

The common ventricle is connected to a common outflow tract. All except the last portion of the separation of the ventricles is achieved by the growth of the muscular interventricular septum. That last portion is done by the **aorticopulmonary septum**, the thing that also divides the truncus arteriosus into the pulmonary artery and pulmonary vein. You saw it in the last figure, but only the tip, and without the ability to see what happened in the truncus arteriosus. That was intentional.

One common outflow tract from one common ventricle into one common truncus arteriosus. You have seen how the interventricular septum separates the ventricles. You know that the aorta exits the heart on the right side of the chest but is connected to the left ventricle, that the pulmonary artery exits the heart on the left side of the chest but is connected to the right ventricle. Regardless of what the aorticopulmonary septum does, the aorta will become the aorta (in the superior mediastinum, it will arch, give off branches, move posterior, perfuse the entire systemic circulation), and the pulmonary artery will become the pulmonary arteries (branch to form four pulmonary arteries, perfuse the pulmonary circulation). Said differently, it does not matter which ventricle the artery is connected to. This is a very important statement. Because the interventricular septum divides the common ventricle into two and divides the outflow tract into two, the truncus arteriosus can't simply be divided into two. If that happens, the left ventricle would be connected to the pulmonary artery, and the right ventricle would be connected to the aorta—backward. So the aorticopulmonary septum that divides the truncus arteriosum must **twist**.

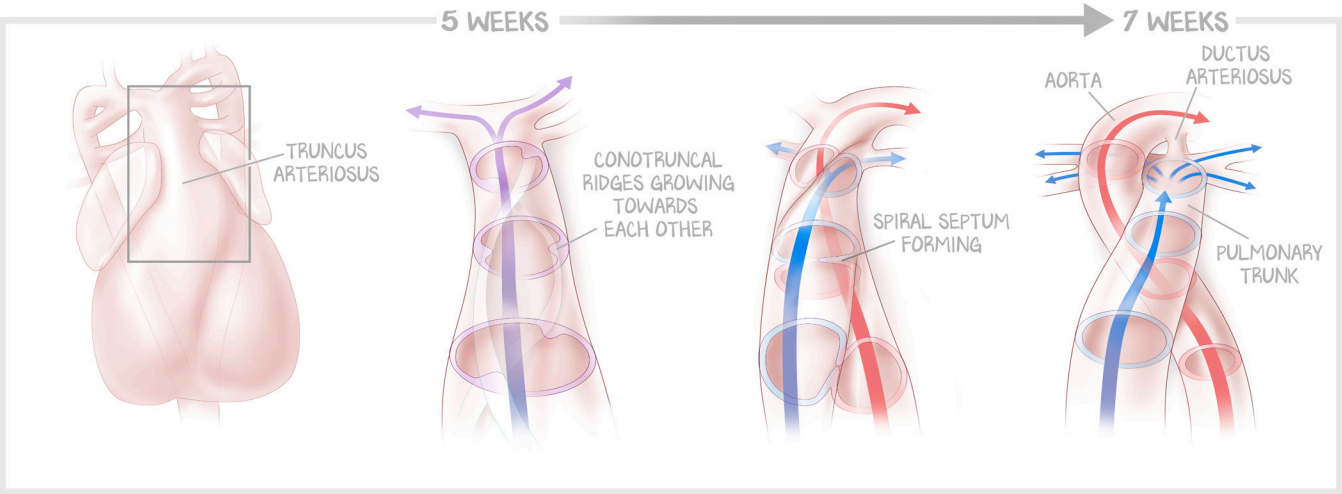

Figure 1.6: Outflow Tract Twist
The development of the aorticopulmonary septum is designed to be constructed in a spiral. Neural crest cells along the length of the truncus arteriosus migrate inward, toward one another. They do so along the length of the truncus arteriosus, but not in the same plane (the spiral is faint—the purple arrow indicates the mixing of blood, and the faint spiral matches the oxygenated red arrow and deoxygenated blue arrow in the subsequent illustrations). The spiraling not only divides the truncus into two vessels but also arranges their position in the outflow tract connected to the right vessel. This also demonstrates why there is an aortic arch and why the ductus arteriosus is where it is—it's a remnant of the truncus arteriosus.

Fetal Circulation

Before we transition to fetal circulation, it is important to realize three things. First, fetal blood is **always deoxygenated** relative to adult blood. Second, **the lungs have high resistance** because the intra-alveolar vessels are either nonexistent or collapsed. The collapsed vessels (low radius, high resistance) ensure that the circulation bypasses the lungs. They are bypassed because the **lungs cannot participate in gas exchange** until week 28. Third, **the placenta is the source of oxygen for the fetus**. We get pretty particular in this section about orientation and directional flow. It's crucial to pay attention to where the most oxygenated blood is coming from and going to, where the deoxygenated blood is, and where the partially oxygenated blood is. To keep things straight, we are going to use the terms high-, medium-, and low-oxygen blood.

High-oxygen blood is the most oxygenated blood the fetus will see. It is less oxygenated than maternal arterial blood, but it is the most oxygenated relative to other states of oxygenation in the fetus. **Medium-oxygen** blood is what happens when high-oxygen blood and low-oxygen blood mixes. **Low-oxygen** blood is the same deoxygenated blood as in the adult—whatever is left over after the tissues use the oxygen in the blood.

Gas exchange occurs at the maternal-fetal circulation—the placenta. Here, baby's **low-oxygen** blood unloads carbon dioxide and picks up oxygen. The now **high-oxygen** blood travels from the placenta to baby's heart via the **umbilical vein**. The umbilical vein branches to feed the portal vein, sending oxygenated blood to the liver. The liver's hepatic vein joins the inferior vena cava. The umbilical vein also connects directly to the inferior vena cava at the **ductus venosus**. Here, the **high-oxygen** blood **mixes** with **low-oxygen** blood, meaning that **medium-oxygen** blood enters the right atrium from the inferior vena cava. The inferior vena cava is oriented so as to project blood directly through the **foramen ovale**, pushing the flap of the septum primum into the atrium. This orientation ensures that the most oxygenated blood—**medium-oxygen** blood—is sent to the left atrium. Left atrium to the left ventricle and up into the aorta. The most oxygenated blood the heart ever sees is oriented to the brain and the upper extremities. Low-oxygen blood returns from the head and arms through the superior vena cava. The superior vena cava is oriented so that the least oxygenated blood the heart sees is directed through the right atrium and tricuspid valve and into the right ventricle. The pulmonary vessels are closed—very high resistance prevents blood flow from the right ventricle into the pulmonary arteries. Instead, the right ventricle pumps blood through the **ductus arteriosus** and into the aorta. This **low-oxygen** blood is directed down the descending aorta, toward the **umbilical arteries**, which carry it to the placenta to be oxygenated. What about the lower part of the body? Not all of the left ventricle's medium-oxygen blood exits through the vessels of the aortic arch. Just as in the adult, blood from the left ventricle is carried in the descending aorta. Technically, this leads to more mixing of medium-oxygen blood with low-oxygen blood, but that level of complexity isn't worth the confusion.

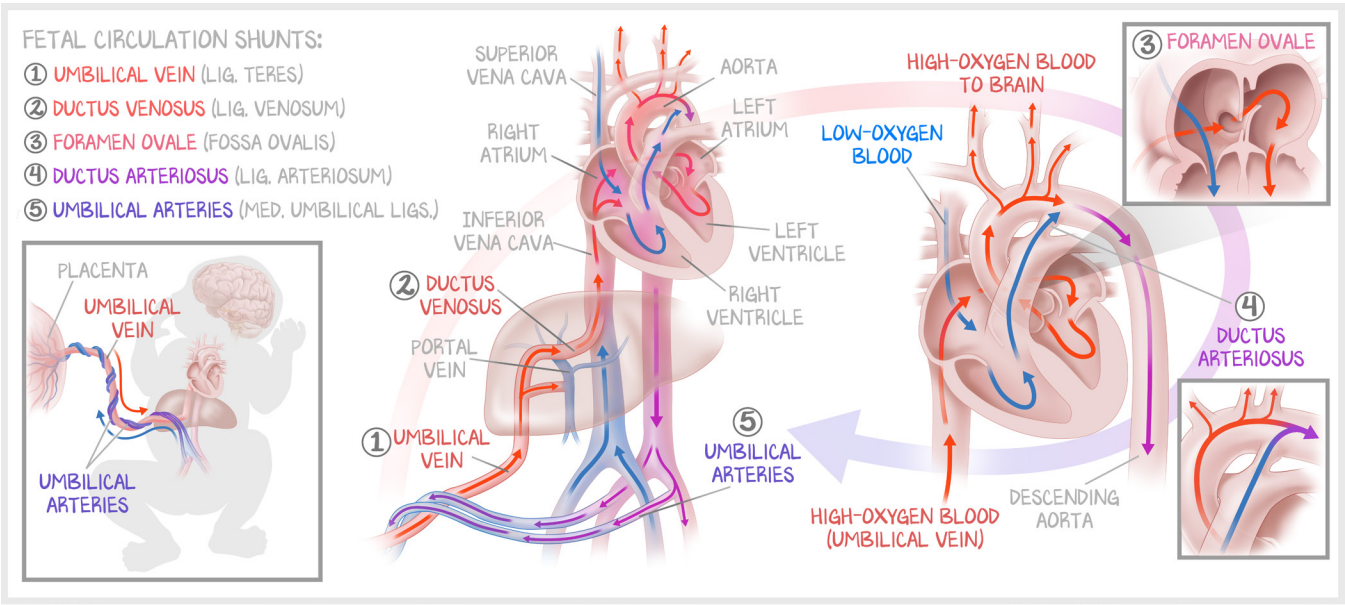

Figure 1.7: Fetal Circulation
For this figure, we have color-coded high-, medium-, and low-oxygen blood: red for high-oxygen, purple for medium-oxygen, and blue for low-oxygen. Oxygenated blood from the placenta is brought back to the fetus by the umbilical vein (1). The portal vein branches from the umbilical vein to perfuse the liver, and the umbilical vein continues as the ductus venosus (2). The ductus venosus connects to the inferior vena cava. Blood returning to the heart from the inferior vena cava is projected through the foramen ovale (3). This orientation ensures that the most oxygenated blood goes to the brain. Oxygenated blood continuing through the descending aorta meets the ductus arteriosus (4), where deoxygenated blood from the right ventricle mixes with the oxygenated blood from the left ventricle. The umbilical arteries (5) carry this mixed, medium-oxygen blood to the placenta in order to be oxygenated.

When baby is born and takes its first breath, the **pulmonary vascular resistance plummets** as the alveoli expand. There must be an immediate shift to neonatal circulation, with closure and reversal of the fetal pathways. The closure of these pathways results in **ligaments**. These ligaments are closed, fibrotic scars of the once patent fetal blood vessels. The **umbilical vein** closes to become the **ligamentum teres** of the liver. The **ductus venosus** closes to become the **ligamentum venosum**. The **foramen ovale** closes due to the reversal of pressure, and the septum primum flap typically fuses to the septum secundum, never to be opened again. The **ductus arteriosus** becomes the **ligamentum arteriosum**. The **umbilical arteries** become the **medial umbilical ligaments**.

The closure of the different ductus is regulated by **oxygen saturation** and **prostaglandins**. The endothelial cells of the ductus arteriosus were only ever exposed to low- or medium-oxygen blood. Now exposed to neonatal high oxygen tensions, the endothelial cells **stop making prostaglandins**. Prostaglandins inhibit the proliferation and contraction of vascular smooth muscle. With high oxygen tension and subsequently low prostaglandins, the vascular smooth muscle cells, the myofibroblasts, contract and proliferate, resulting in vasoconstriction and fibrotic elimination of the ductus arteriosus. **Oxygen closes the ductus. Prostaglandins keep the ductus open.** NSAIDs, as we will see in congenital heart defects, close it.

FETAL STRUCTURE	ADULT STRUCTURE	CLINICAL SIGNIFICANCE
Ductus arteriosus	Ligamentum arteriosum	Tears aorta in deceleration injuries
Ductus venosus	Ligamentum venosum	Tears liver in deceleration injuries
Umbilical artery	Round ligament of liver	None
Umbilical vein	Medial umbilical ligament	Inadequate closure can result in pathologies; discussed in Renal

Table 1.1: Fetal Circulation and Ligaments
What they are in the fetus and the adult, and what clinical disease can arise as an adult.